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1,3 -disubstituted urea derivatives, useful as inhibitors of acyl co-enzyme A cholesterol acyl transferase enzyme

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AU 9916976	A	19990712	AU 9916976	A	19981216	199950
EP 1042278	A1	20001011	EP 98961715	A	19981216	200052
			WO 98SK19	A	19981216	
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Abstract (Basic): WO 9932437 A1

NOVELTY - Novel 1,3-disubstituted ureas are inhibitors of acyl co-enzyme A: cholesterol acyl transferase (ACAT) enzyme, and can inhibit cholesterol esterification and absorption in hypercholesterolemia.

DETAILED DESCRIPTION - 1,3-disubstituted ureas of formula (I) are new.

When R1=2-fluorophenyl, 2,4- or 2,5-difluorophenyl, 2-chlorophenyl, 2,3-, 2,6- or 3,5-dichlorophenyl, 2- or 4-methylphenyl, 2,4-, 2,6- or 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-pyridyl, 1- or 2-naphthyl or

1-adamantyl, then R2=NO₂, and X=O;
when R1=groups as above and 4-nitrophenyl, 4-fluorophenyl,
4-chlorophenyl, 2,4- or 3,4-dichlorophenyl, then R2=NO₂ and X=S;
when R1=2,4-difluorophenyl, 2,3-dichlorophenyl, or
2,6-di(methylethyl)phenyl, then R2=amino; and X=O or S.

ACTIVITY - Anti-hypercholesterolemia.

MECHANISM OF ACTION - ACAT inhibitors. The percentages of ACAT inhibition by compounds (I), at concentration 2 mM, was up to 88% in rats' liver, and up to 71% in rabbits' intestinal mucosa.

USE - (I) are used for treating hypercholesterolemia and preventing atherosclerosis.

pp; 33 DwgNo 0/0

Title Terms: DISUBSTITUTED; UREA; DERIVATIVE; USEFUL; INHIBIT; ACYL; CO; ENZYME; CHOLESTEROL; ACYL; TRANSFERASE; ENZYME

Derwent Class: B05

International Patent Class (Main): C07C-273/18; C07C-275/30; C07C-275/36

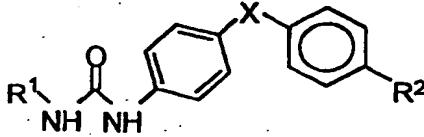
International Patent Class (Additional): A61K-031/17; A61K-031/44;

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(54) Title: 1,3-DISUBSTITUTED UREAS AS ACAT INHIBITORS, AND METHOD OF PREPARING THEREOF			
(57) Abstract			
<p>The invention relates to 1,3-disubstituted ureas of general formula (I) where R¹ is an aryl, R² is nitro and/or amino, and X is oxygen and/or sulfur, and the method of preparing thereof which consists in treating aromatic amines with isocyanates. Isocyanates may be formed in situ and the reaction carried out in toluene, at 80 °C. If the nitro group is formed, it is reduced with hydrogen in the presence of palladium catalyst to the amino group. The obtained 1,3-disubstituted ureas are inhibitors of the activity of the acyl co-enzyme A: cholesterol acyltransferase (ACAT) enzyme, and may be used to inhibit cholesterol esterification and absorption in hypercholesterolemia.</p>			
 (I)			

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1,3-Disubstituted Ureas as ACAT Inhibitors, and Method of Preparing Thereof**Technical Field**

The invention relates to compounds the principal characteristics of which include inhibition of the acyl-coenzyme A: cholesterol acyltransferase (ACAT) enzyme activity, and to a method for the preparation of such compounds.

Background Art

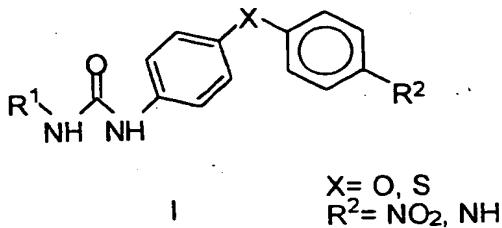
The acyl-coenzyme A: cholesterol O-acyltransferase (EC 2.3.1.26) (ACAT) enzyme is responsible for the catalysis of the intracellular esterification of cholesterol. ACAT is present in most tissues such as the intestine, liver, and arterial wall. The enzyme is assumed to be involved in numerous processes which underlie the development of atherosclerosis, absorption of dietary cholesterol, accumulation of cholesterol esters, hepatic secretion of cholesterol esters into the blood plasma in the form of VLDL cholesterol.

A number of substances of the urea type have been described to inhibit ACAT. We shall show several more recent examples describing 1,3-disubstituted ureas as ACAT enzyme inhibitors. Patents EP 506532, FR 2674522, JP 93097802, US 5219859 describe ureas containing indole derivatives in their molecules. A combination of aromatic and aliphatic moieties has been described in Patents EP 665216, JP 95258199. Introduction into the molecule of a 1,3-dioxolane ring has been reported in *Bioorg. Med. Chem. Lett.* 1995, 5(15): 1581.

1,3-Disubstituted ureas of the present invention have not been described in literature.

Disclosure of Invention

1,3-Disubstituted ureas of general formula I,



wherein R^1 is 4-nitrophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R^2 is nitro, and $X = O, S$; and for R^1 being 2,4-difluorophenyl, 2,3-dichlorophenyl, 2,6-dimethylphenyl, 2,6-di(methylethyl)-phenyl R^2 is amino, and $X = O, S$.

The method for the preparation of the above compounds according to this invention consists in reacting an isocyanate (as prepared in situ or as commercially available) with amine to give an urea the nitro group of which may subsequently be reduced to the amino group. Ureas prepared in this way show inhibitory effect on acyl-coenzyme A: cholesterol acyltransferase (ACAT).

Examples

Example 1

1-(4-Nitrophenyl)-3-((4-nitrophenoxy)-phenyl)-urea

A solution of 4-nitrophenylisocyanate in diethylether (20 ml) is added dropwise to a solution of 4'-nitrophenoxy-aniline (2.30 g, 0.01 mol) in a mixture of diethylether (20 ml) and tetrahydrofuran (20 ml) at laboratory temperature, and the mixture is stirred for 16 hours. The precipitated product is aspirated, washed with diethylether (20 ml). The raw product is purified by chromatography on silica gel eluting with dichloromethane-methanol.

¹H-NMR (CDCl₃): 7.11(d, 2H, H-arom.); 7.17(d, 2H, H-arom.); 7.59(d, 2H, H-arom.); 7.70(d, 2H, H-arom.); 8.20(d, 2H, H-arom.); 7.25(d, 2H, H-arom.); 9.05(s, 1H, NH.); 9.46(s, 1H, NH).

¹³C-NMR (CDCl₃): 116.80(CH-arom.); 117.46(CH-arom.); 120.46(CH-arom.); 121.13(CH-arom.); 125.07(CH-arom.); 126.11(CH-arom.); 136.50, 141.00, 141.96, 146.26, 148.86, 151.95(C-arom.); 163.39(C = O).

Analysis for C₁₈H₁₄N₄O₆

%C(calcd/found)	%H	%N
57.85/57.73	3.58/3.61	14.21/14.12

Yield: 92% Melting temp.: 231-234°C

Example 2

1-(2-Fluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2-fluorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for C₁₈H₁₄FN₃O₄

%C(calcd/found)	%H	%N
62.11/62.09	3.84/3.88	11.44/11.29

Yield: 48% Melting temp.: 253-255°C

Example 3

1-(4-Fluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-fluorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{14}FN_3O_4$

%C(calcd/found)	%H	%N
62.11/61.99	3.84/3.85	11.44/11.34

Yield: 59% Melting temp.: 267-269°C

Example 4

1-(2,4-Difluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,4-difluorophenylisocyanate by an analogous procedure to that described in Example 1.

1H -NMR ($CDCl_3$): 6.98-7.18(m, 5H, H-arom.); 7.23-7.37(m, 1H, H-arom.); 7.56(d, 2H, H-arom.); 8.03-8.16(m, 1H, H-arom.); 8.24(d, 2H, H-arom.); 8.50(s, 1H, NH); 9.13(s, 1H, NH).

^{13}C -NMR ($CDCl_3$): 103.72(CH-arom.); 110.96(CH-arom.); 116.73(CH-arom.); 119.88(CH-arom.); 121.18(CH-arom.); 122.02(CH-arom.); 126.09(CH-arom.); 136.94, 141.91, 148.48, 152.27, 154.49, 159.80(C-arom.); 163.46(C=O).

Analysis for $C_{18}H_{13}F_2N_3O_4$

%C(calcd/found)	%H	%N
59.22/59.20	3.40/3.53	10.91/10.89

Yield: 85% Melting temp.: 223-224°C

Example 5

1-(2,5-Difluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,5-difluorophenylisocyanate by an analogous procedure to that described in Example 1.

1H -NMR ($CDCl_3$): 6.73-6.88(m, 1H, H-arom.); 7.04-7.35(m, 5H, H-arom.); 7.56(d, 2H, H-arom.); 7.98-8.11(m, 1H, H-arom.); 8.22(d, 2H, H-arom.); 8.75-9.30(br.s., 2H, NH).

^{13}C -NMR ($CDCl_3$): 106.56(CH-arom.); 107.75(CH-arom.); 115.67(CH-arom.); 116.74(CH-arom.); 120.03(CH-arom.); 121.21(CH-arom.); 126.08(CH-arom.); 128.82, 136.62, 141.95, 148.73, 151.95, 155.65, 160.38(C-arom.); 163.42(C=O).

Analysis for $C_{10}H_{13}F_2N_3O_4$

%C(calcd/found)	%H	%N
59.22/59.07	3.40/3.49	10.91/10.83

Yield: 76% Melting temp.: 207-208°C

Example 6

1-(2,6-Difluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-difluorophenylisocyanate by an analogous procedure to that described in Example 1.

1H -NMR ($CDCl_3$): 6.95-7.26(m, 6H, H-arom.); 7.42-7.56(m, 2H, H-arom.); 8.01-8.23(m, 3H, H-arom.); 8.94-9.05(m, 2H, NH).

^{13}C -NMR ($CDCl_3$): 111.77(CH-arom.); 116.82(CH-arom.); 120.06(CH-arom.); 121.18(CH-arom.); 126.19(CH-arom.); 127.11(CH-arom.); 137.31, 141.99, 148.49, 152.61, 155.65, 160.57(C-arom.); 163.61(C=O).

Analysis for $C_{10}H_{13}F_2N_3O_4$

%C(calcd/found)	%H	%N
59.22/59.10	3.40/3.55	10.91/10.78

Yield: 75% Melting temp.: 231-232°C

Example 7

1-(2-Chlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2-chlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{10}H_{14}ClN_3O_4$

%C(calcd/found)	%H	%N	%Cl
59.46/59.37	3.68/3.82	10.95/10.78	9.24/8.99

Yield: 63% Melting temp.: 195-197°C

Example 8

1-(4-Chlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-chlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{14}ClN_3O_4$

%C(calcd/found)	%H	%N	%Cl
59.46/59.37	3.68/3.77	10.95/10.84	9.24/9.02

Yield: 69% Melting temp.: 234-236°C

Example 9

1-(2,3-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,3-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.50	3.13/3.31	10.05/9.78	16.95/16.91

Yield: 74% Melting temp.: 199-201°C

Example 10

1-(2,4-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.49	3.13/3.21	10.05/9.80	16.95/16.59

Yield: 71% Melting temp.: 267-269°C

Example 11

1-(2,6-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.39	3.13/3.20	10.05/9.92	16.95/16.81

Yield: 68% Melting temp.: 195-198°C

Example 12**1-(3,4-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 3,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.49	3.13/3.23	10.05/9.89	16.95/16.78

Yield: 80% Melting temp.: 179-180°C

Example 13**1-(3,5-Dichlorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 3,5-dichlorophenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{18}H_{13}Cl_2N_3O_4$

%C(calcd/found)	%H	%N	%Cl
54.56/54.48	3.13/3.30	10.05/10.01	16.95/17.24

Yield: 56% Melting temp.: 213-216°C

Example 14**1-(2-Methylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 2-methylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{20}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
60.11/65.96	4.72/4.89	11.56/11.48

Yield: 59% Melting temp.: 112-116°C

Example 15**1-(4-Methylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 4-methylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{20}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
66.11/66.02	4.72/4.87	11.56/11.40

Yield: 64% Melting temp.: 168-170°C

Example 16

1-(2,4-Dimethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,4-dimethylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{21}H_{19}N_3O_4$

%C(calcd/found)	%H	%N
66.83/66.87	5.07/5.10	11.13/11.05

Yield: 73% Melting temp.: 165-169°C

Example 17

1-(2,6-Dimethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-dimethylphenylisocyanate by an analogous procedure to that described in Example 1.

1H -NMR ($CDCl_3$): 2.22(s, 6H, CH_3); 7.04-7.17(m, 7H, H-arom.); 7.57(m, 2H, H-arom.); 7.74(s, 1H, NH); 8.23(d, 2H, H-arom.); 8.87(s, 1H, NH).

^{13}C -NMR ($CDCl_3$): 18.19(2x CH_3); 116.61(CH-arom.); 119.54(CH-arom.); 121.08(CH-arom.); 126.07(CH-arom.); 127.67(CH-arom.); 135.53(CH-arom.); 125.93, 135.51, 137.95, 141.82, 147.87, 153.10(CH-arom.); 163.64(C=O).

Analysis for $C_{21}H_{19}N_3O_4$

%C(calcd/found)	%H	%N
66.83/66.67	5.07/5.18	11.13/10.98

Yield: 68% Melting temp.: 249-250°C

Example 18

1-(3,5-Dimethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 3,5-dimethylphenylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{21}H_{19}N_3O_4$

%C(calcd/found)	%H	%N
66.83/66.78	5.07/5.22	11.13/11.06

Yield: 58% Melting temp.: 145-147°C

Example 19

1-(2,6-Di-(methylethyl)-phenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 2,6-di-(methylethyl)phenylisocyanate by an analogous procedure to that described in Example 1.

¹H-NMR (CDCl₃): 1.18(d, 6H, 2xCH₃); 3.22(hept., 2H, 2xCH); 7.06-7.30(m, 7H, H-arom.); 7.56(d, 2H, H-arom.); 7.63(s, 1H, NH); 8.23(d, 2H, H-arom.); 8.78(s, 1H, NH).

¹³C-NMR (CDCl₃): 23.31(2xCH₃); 27.86(2xCH); 116.58(CH-arom.); 119.44(CH-arom.); 120.86(CH-arom.); 122.72(CH-arom.); 125.87(CH-arom.); 146.53(CH-arom.); 127.08, 132.14, 137.80, 141.83, 147.89, 154.10(C-arom.); 163.46(C=O).

Analysis for C₂₆H₂₇N₃O₄

%C(calcd/found)	%H	%N
69.27/69.13	6.28/6.34	9.69/9.56

Yield: 88% Melting temp.: 208-210°C

Example 20

1-(2-Trifluoromethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea

4'-Nitrophenoxy-aniline (1.0 g, 4.3 mmol), triphosgene (0.43 g, 1.44 mmol), triethylamine (0.6 ml, 4.3 mmol) are heated in toluene (15 ml) in a pressure tube at 80°C for 20 hours. Then, 2-trifluoromethylaniline (0.53 ml, 4.3 mmol) and triethylamine (0.6 ml, 4.3 mmol) in toluene (10 ml) are added. The mixture is heated at 80°C for 4 hours, then it is concentrated, and the product is isolated using chromatography on silica gel eluting with dichloromethane - methanol.

Analysis for C₂₀H₁₄F₃N₃O₄

%C(calcd/found)	%H	%N
57.56/57.60	3.38/3.44	10.07/9.89

Yield: 67% Melting temp.: 201-203°C

Example 21**1-(3-Trifluoromethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 3-trifluoromethylaniline by an analogous procedure to that described in Example 20.

Analysis for $C_{20}H_{14}F_3N_3O_4$

%C(calcd/found)	%H	%N
57.56/57.66	3.38/3.45	10.07/9.96

Yield: 72% Melting temp.: 208-211°C

Example 22**1-(4-Trifluoromethylphenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 4-trifluoromethylaniline by an analogous procedure to that described in Example 20.

Analysis for $C_{20}H_{14}F_3N_3O_4$

%C(calcd/found)	%H	%N
57.56/57.48	3.38/3.41	10.07/10.00

Yield: 45% Melting temp.: 185-189°C

Example 23**1-(2-Pyridyl)-3-(4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 2-pyridylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{18}H_{14}N_4O_4$

%C(calcd/found)	%H	%N
61.71/61.67	4.03/4.06	15.99/15.79

Yield: 76% Melting temp.: 143-146°C

Example 24**1-(3-Pyridyl)-3-(4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 3-pyridylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{18}H_{14}N_4O_4$

%C(calcd/found)	%H	%N
61.71/61.58	4.03/4.21	15.99/15.87

Yield: 69% Melting temp.: 177-179°C

Example 25

1-(4-Pyridyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 4-pyridylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{18}H_{14}N_4O_4$

%C(calcd/found)	%H	%N
61.71/61.66	4.03/4.11	15.99/15.87

Yield: 72% Melting temp.: 126-127°C

Example 26

1-(1-Naphthyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 1-naphthylisocyanate by an analogous procedure to that described in Example 1.

Analysis for $C_{23}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
69.17/69.23	4.29/4.41	10.52/10.46

Yield: 82% Melting temp.: 117-119°C

Example 27

1-(2-Naphthyl)-3-(4'-nitrophenoxy)-phenyl)-urea

The title compound was prepared from 1-naphthylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{23}H_{17}N_3O_4$

%C(calcd/found)	%H	%N
69.17/69.09	4.29/4.36	10.52/10.38

Yield: 69% Melting temp.: 103-106°C

Example 28**1-(1-Adamantyl)-3-(4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 1-adamantylamine by an analogous procedure to that described in Example 20.

Analysis for $C_{23}H_{25}N_3O_4$.

%C(calcd/found)	%H	%N
67.80/67.65	6.18/6.23	10.31/10.16

Yield: 61% Melting temp.: 143-146°C

Example 29**1-(4-Nitrophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

A solution of 4-nitrophenylisocyanate in diethylether (20 ml) is added dropwise to a solution of 4'-nitrophenoxy-aniline (2.46 g, 0.01 mol) in a mixture of diethylether (20 ml) and tetrahydrofuran (20 ml) at laboratory temperature, and the mixture is stirred for 16 hours. The resulting product is aspirated, washed with diethylether (20 ml). The crude product is purified by chromatography on silica gel eluting with dichloromethane and methanol.

Analysis for $C_{19}H_{14}N_4O_5S$

%C(calcd/found)	%H	%N	S%
55.61/55.52	3.44/3.49	13.65/13.59	7.81/7.67

Yield: 56% Melting temp.: 164-167°C

Example 30**1-(2-Fluorophenyl)-3-((4'-nitrophenoxy)-phenyl)-urea**

The title compound was prepared from 2-fluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{14}FN_3O_5S$

%C(calcd/found)	%H	%N	S%
59.52/59.41	3.68/3.77	10.96/11.04	8.36/8.41

Yield: 61% Melting temp.: 274-277°C

Example 31**1-(4-Fluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 4-fluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{14}FN_3O_3S$

%C(calcd/found)	%H	%N	S%
59.52/59.46	3.68/3.71	10.96/10.87	8.36/8.18

Yield: 59% Melting temp.: 287-290°C

Example 32**1-(2,4-Difluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,4-difluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}F_2N_3O_3S$

%C(calcd/found)	%H	%N	S%
56.86/56.78	3.26/3.39	10.47/10.41	7.99/7.86

Yield: 57% Melting temp.: 268-271°C

Example 33**1-(2,5-Difluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,5-difluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}F_2N_3O_3S$

%C(calcd/found)	%H	%N	S%
56.86/56.76	3.26/3.37	10.47/10.35	7.99/8.05

Yield: 64% Melting temp.: 259-261°C

Example 34**1-(2,6-Difluorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,6-difluorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}F_2N_3O_3S$

%C(calcd/found)	%H	%N	S%
56.86/56.69	3.26/3.34	10.47/10.43	7.99/7.81

Yield: 68% Melting temp.: 263-265°C

Example 35

1-(2-Chlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-chlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{18}H_{14}ClN_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
57.07/57.01	3.53/3.62	10.51/11.46	8.87/8.65	8.02/7.95

Yield: 65% Melting temp.: 231-233°C

Example 36

1-(4-Chlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-chlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{14}ClN_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
57.07/56.97	3.53/3.57	10.51/10.45	8.87/8.81	8.02/7.86

Yield: 63% Melting temp.: 206-209°C

Example 37

1-(2,3-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,3-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{19}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.46	3.02/3.07	9.68/9.62	16.33/16.27	7.38/7.50

Yield: 75% Melting temp.: 157-159°C

Example 38**1-(2,4-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{18}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.57	3.02/3.21	9.68/9.54	16.33/16.35	7.38/7.28

Yield: 57% Melting temp.: 174-178°C

Example 39**1-(2,6-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,6-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{18}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.51	3.02/3.07	9.68/9.73	16.33/16.25	7.38/7.19

Yield: 83% Melting temp.: 164-167°C

Example 40**1-(3,4-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 3,4-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{18}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.47	3.02/3.14	9.68/9.57	16.33/16.09	7.38/7.24

Yield: 57% Melting temp.: 238-240°C

Example 41**1-(3,5-Dichlorophenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 3,5-dichlorophenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{18}H_{13}Cl_2N_3O_3S$

%C(calcd/found)	%H	%N	%Cl	S%
52.55/52.47	3.02/3.11	9.68/9.59	16.33/16.21	7.38/7.41

Yield: 67% Melting temp.: 185 - 188°C

Example 42

1-(2-Methylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-methylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{20}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
63.31/63.22	4.52/4.66	11.07/10.79	8.45/8.34

Yield: 78% Melting temp.: 229-234°C

Example 43

1-(4-Methylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-methylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{20}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
63.31/63.25	4.52/4.63	11.07/11.12	8.45/8.35

Yield: 73% Melting temp.: 163-166°C

Example 44

1-(2,4-Dimethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2,4-dimethylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{21}H_{19}N_3O_3S$

%C(calcd/found)	%H	%N	S%
64.11/64.08	4.87/4.83	10.68/10.59	8.15/7.95

Yield: 65% Melting temp.: 209-213°C

Example 45**1-(2,6-Dimethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,6-dimethylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{21}H_{19}N_3O_3S$

%C(calcd/found)	%H	%N	S%
64.11/63.97	4.87/4.83	10.68/10.47	8.15/8.01

Yield: 72% Melting temp.: 264-267°C

Example 46**1-(3,5-Dimethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 3,5-dimethylphenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{21}H_{19}N_3O_3S$

%C(calcd/found)	%H	%N	S%
64.11/64.04	4.87/4.99	10.68/10.63	8.15/8.01

Yield: 68% Melting temp.: 194-196°C

Example 47**1-(2,6-Dimethylethyl)-phenyl-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2,6-(methylethyl)-phenylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{26}H_{27}N_3O_3S$

%C(calcd/found)	%H	%N	S%
66.79/66.72	6.06/6.17	9.35/9.27	7.12/6.96

Yield: 72% Melting temp.: 175-177°C

Example 48**1-(2-Trifluoromethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

4'-Nitrophenylthio-aniline (1.06 g, 4.3 mmol), triphosgene (0.43 g, 1.44 mmol), triethylamine (0.6 g, 4.3 mmol) in toluene (15 ml) are heated in a pressure tube at 80°C for 20 hours. Subsequently, 2-trifluoromethylaniline (0.53 ml, 4.3 mmol)

and triethylamine (0.6 ml, 4.3 mmol) in toluene (10 ml) are added. The mixture is heated at 80°C for 4 hours, then concentrated, and the product is separated by chromatography on silica gel eluting with dichloromethane-methanol.

Analysis for $C_{20}H_{14}F_3N_3O_3S$

%C(calcd/found)	%H	%N	S%
55.43/55.38	3.26/3.39	9.70/9.71	7.40/7.35

Yield: 52% Melting temp.: 257-261 °C

Example 49

1-(3-Trifluoromethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 3-trifluorophenylisocyanate by an analogous procedure to that described in Example 48.

Analysis for $C_{20}H_{14}F_3N_3O_3S$

%C(calcd/found)	%H	%N	S%
55.43/55.21	3.26/3.38	9.70/9.53	7.40/7.31

Yield: 65% Melting temp.: 241-244 °C

Example 50

1-(4-Trifluoromethylphenyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 4-trifluorophenylisocyanate by an analogous procedure to that described in Example 48.

Analysis for $C_{20}H_{14}F_3N_3O_3S$

%C(calcd/found)	%H	%N	S%
55.43/55.37	3.26/3.33	9.70/9.81	7.40/7.28

Yield: 51% Melting temp.: 254-257 °C

Example 51

1-(2-Pyridyl)-3-((4'-nitrophenylthio)-phenyl)-urea

The title compound was prepared from 2-pyridylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{18}H_{14}N_4O_3S$

%C(calcd/found)	%H	%N	S%
59.01/58.86	3.85/3.91	15.29/15.23	8.75/8.80

Yield: 48% Melting temp.: 278-281°C

Example 52**1-(3-Pyridyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 3-pyridylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{18}H_{14}N_4O_3S$

%C(calcd/found)	%H	%N	S%
59.01/58.99	3.85/3.99	15.29/15.25	8.75/8.49

Yield: 63% Melting temp.: 261-264°C

Example 53**1-(4-Pyridyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 4-pyridylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{18}H_{14}N_4O_3S$

%C(calcd/found)	%H	%N	S%
59.01/58.92	3.85/3.76	15.29/15.32	8.75/8.67

Yield: 69% Melting temp.: 190-192°C

Example 54**1-(1-Naphthyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 1-naphthylisocyanate by an analogous procedure to that described in Example 29.

Analysis for $C_{23}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
66.49/66.53	4.13/4.21	10.12/10.17	7.70/7.54

Yield: 56% Melting temp.: 164-168°C

Example 55**1-(2-Naphthyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 2-naphthylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{23}H_{17}N_3O_3S$

%C(calcd/found)	%H	%N	S%
66.49/66.47	4.13/4.25	10.12/10.06	7.70/7.57

Yield: 69% Melting temp.: 142-147°C

Example 56**1-(1-Adamantyl)-3-((4'-nitrophenylthio)-phenyl)-urea**

The title compound was prepared from 1-adamantylamine by an analogous procedure to that described in Example 48.

Analysis for $C_{23}H_{25}N_3O_3S$

%C(calcd/found)	%H	%N	S%
65.22/65.17	5.95/6.03	9.93/10.02	7.56/7.38

Yield: 52% Melting temp.: 264-267°C

Example 57**1-(2,4-Difluorophenyl)-3-((4'-aminophenoxy)-phenyl)-urea**

One gram of compound 4 is dissolved in methanol (20 ml) and 0.1 g of 10% palladium on charcoal is added. The mixture is stirred under hydrogen atmosphere (at atmospheric pressure) for 20 hours. Subsequently, 100 ml methanol is added and the catalyst is removed by filtering. The product is then obtained by concentrating the methanolic solution.

Analysis for $C_{19}H_{15}F_2N_3O_2$

%C(calcd/found)	%H	%N
64.22/64.09	4.25/4.29	11.83/12.01

Yield: 88% Melting temp.: 248-251°C

Example 58**1-(2,5-Dichlorophenyl)-3-((4'-aminophenoxy)-phenyl)-urea**

The title compound was prepared from compound 9 by an analogous procedure to that described in Example 57.

Analysis for $C_{19}H_{15}Cl_2N_3O_2$

%C(calcd/found)	%H	%N	%Cl
58.78/58.45	3.89/3.94	10.82/10.78	18.26/18.11

Yield: 91% Melting temp.: 201-204°C

Example 59

1-(2,6-Dimethylphenyl)-3-((4'-aminophenoxy)-phenyl)-urea

The title compound was prepared from compound 17 by an analogous procedure to that described in Example 57.

Analysis for $C_{21}H_{21}N_3O_2$

%C(calcd/found)	%H	%N
72.60/72.45	6.09/6.13	12.10/12.02

Yield: 85% Melting temp.: 225-227°C

Example 60

1-(2,6-Di(methylethyl)-phenyl)-3-((4'-aminophenoxy)-phenyl)-urea

The title compound was prepared from compound 19 by an analogous procedure to that described in Example 57.

1H -NMR ($CDCl_3$): 1.15(d, 6H, 2xCH₃); 3.15(hept., 2H, 2xCH); 4.86(s, 2H, NH); 6.57(d, 2H, H-arom.); 6.72(d, 2H, H-arom.); 6.81(d, 2H, H-arom.); 7.10-1.28(m, 3H, H-arom.); 7.36(d, 2H, H-arom.); 7.56(s, 1H, HN); 8.58(br.s., 1H, NH).

^{13}C -NMR ($CDCl_3$): 23.43(2xCH₃); 27.93(2xCH); 114.63(CH-arom.); 117.55(CH-arom.); 119.09(CH-arom.); 199.43(CH-arom.); 122.79(CH-arom.); 127.11(CH-arom.); 127.11(CH-arom.); 132.40, 134.86, 144.77, 146.61, 146.89, 152.88(C-arom.); 154.36(C=O).

Analysis for $C_{26}H_{29}N_3O_2$

%C(calcd/found)	%H	%N
74.41/74.54	7.24/7.33	10.41/10.34

Yield: 90% Melting temp.: 219-221°C

Example 61**1-(2,4-Difluorophenyl)-3-((4'-aminophenylthio)-phenyl)-urea**

The title compound was prepared from compound 32 by an analogous procedure to that described in Example 57.

Analysis for $C_{19}H_{16}F_2N_3OS$

%C(calcd/found)	%H	%N	%S
61.44/61.56	4.07/4.18	11.31/11.15	8.63/8.51

Yield: 79% Melting temp.: exceeding 300°C

Example 62**1-(2,3-Dichlorophenyl)-3-((4'-aminophenylthio)-phenyl)-urea**

The title compound was prepared from compound 37 by an analogous procedure to that described in Example 57.

Analysis for $C_{19}H_{15}Cl_2N_3OS$

%C(calcd/found)	%H	%N	%Cl	%S
56.44/56.35	3.74/3.80	10.39/10.41	17.54/17.57	7.93/7.59

Yield: 88% Melting temp.: 259-261°C

Example 63**1-(2,6-Dimethylphenyl)-3-((4'-aminophenylthio)-phenyl)-urea**

The title compound was prepared from compound 45 by an analogous procedure to that described in Example 57.

Analysis for $C_{21}H_{21}N_3OS$

%C(calcd/found)	%H	%N	%S
69.39/69.32	5.82/5.93	11.56/11.49	8.28/8.54

Yield: 94% Melting temp.: 198-202°C

Example 64**1-(2,6-Di-(methylethyl)-phenyl-3-((4'-aminophenylthio)-phenyl)-urea**

The title compound was prepared from compound 47 by an analogous procedure to that described in Example 57.

Analysis for $C_{26}H_{28}N_3OS$

%C(calcd/found)	%H	%N	%S
71.56/71.55	6.97/6.89	10.01/10.11	7.64/7.58

Yield: 83% Melting temp.: 267-271°C

Tests

The biological activity of the substances was evaluated based on the in vitro inhibition of acylCoa:cholesterol acyltransferase (ACAT) activity. The enzyme was obtained from the microsomal fraction of rat liver cells and rabbit intestinal mucosa of animals fed with cholesterol. The substrates for the enzyme reaction included exogenous oleoyl co-enzyme A and endogenous cholesterol. ^{14}C -oleoyl co-enzyme A conversion to ^{14}C -cholesteryl oleate was monitored. From the mixture of extracted lipids, cholesteryl oleate was separated using thin-layer chromatography, and was quantified radiometrically. ACAT specific activity was expressed as the amount of cholesteryl oleate formed per minute per mg microsomal protein.

Table 1 shows percentages of ACAT inhibition in the rat liver and the rabbit intestinal mucosa at various concentrations of the substances tested. Efficiency was calculated as compared to enzyme activity measured in the presence of 1% dimethylsulfoxide used as the solvent to prepare solutions of the substances tested.

Table 1

Inhibitory effect on rat liver and rabbit intestinal mucosa ACAT activity

No	Efficiency (%)		Concentration (μM)	No	Efficiency (%)		Concentration (μM)
	<i>liver</i>	<i>mucosa</i>			<i>liver</i>	<i>mucosa</i>	
1	0	46	2	33	0	16	2
2	15	32	2	34	11	25	2
3	0	24	2	35	20	26	2
4	37	55	2	36	12	21	2
5	49	58	2	37	0	0	2
6	0	42	2	38	12	16	2
7	0	0	2	39	15	21	2
8	17	13	2	40	0	20	2
9	58	51	2	41	0	0	2
10	10	26	2	42	27	31	2
11	20	25	2	43	21	32	2
12	11	57	2	44	19	31	2
13	0	0	2	45	23	34	2
14	0	0	2	46	18	27	2
15	0	0	2	47	88	71	2
16	0	0	2	48	25	38	2
17	41	65	2	49	34	45	2
18	0	0	2	50	23	25	2
19	50	67	2	51	48	46	2
20	46	42	2	52	45	36	2
21	38	45	2	53	53	35	2
22	25	18	2	54	24	36	2
23	26	34	2	55	16	31	2
24	0	0	2	56	45	56	2
25	11	17	2	57	53	64	2
26	14	22	2	58	55	46	2

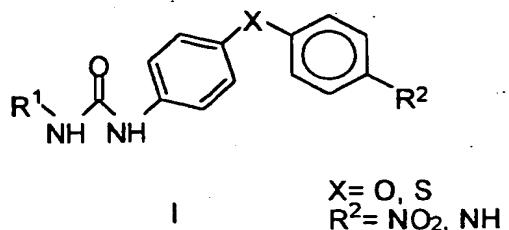
27	0	12	2	59	38	62	2
28	43	58	2	60	68	64	2
29	0	34	2	61	22	25	2
30	0	23	2	62	15	26	2
31	25	27	2	63	21	29	2
32	16	23	2	64	56	67	2

Industrial Applicability

The compounds according to the invention and the method of preparing thereof can be used in pharmaceutical production to make preparations with inhibitory effect on the enzyme acyl co-enzyme A and on cholesterol absorption in hypercholesterolemia.

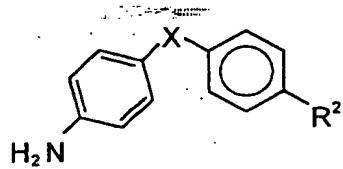
C L A I M S

1. 1,3-Disubstituted ureas of general formula I,



wherein R¹ is 4-nitrophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R² is nitro, and X = O, S; and for R¹ being 2,4-difluorophenyl, 2,3-dichlorophenyl, 2,6-dimethylphenyl, 2,6-di(methylethyl)-phenyl R² is amino, and X = O, S.

2. A method of preparing 1,3-disubstituted ureas of general formula I according to claim 1, characterized in that an amine of general formula II,



wherein R² and X have the above defined meanings, is treated with an isocyanate of general formula III,



III

wherein R¹ has the above defined meaning, said isocyanate optionally being formed in situ from appropriate reactants,

thus giving the above defined urea.

3. The method of claim 2, characterized in that when said isocyanate is formed in situ, the reaction is carried out in toluene at about 80°C.

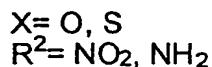
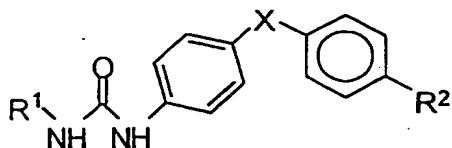
4. The method of any of the preceding claims, characterized in that the obtained 1,3-disubstituted urea of general formula I wherein R² means nitro, is treated with hydrogen in the presence of palladium catalyst to reduce the nitro group to the amino group.

5. 1,3-Disubstituted ureas of general formula I, according to claim 1 and/or prepared by the method of claim 2 to 4, characterized in that they have inhibitory effect on the acyl co-enzyme A:cholesterol acyltransferase (ACAT) enzyme.

AMENDED CLAIMS

[received by the International Bureau on 08 June 1999 (08.06.99);
original claim 1 amended remaining claims unchanged (2 pages)]

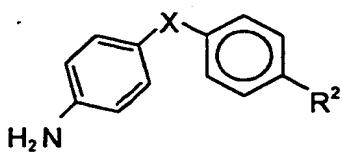
1. 1,3-Disubstituted ureas of general formula I,



wherein R^1 is 2-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 2,3-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R^2 is nitro, and $X = O$;
wherein R^1 is 4-nitrophenyl, 2-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 3,5-dimethylphenyl, 2,6-di(methylethyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 1-adamantyl, and R^2 is nitro, and $X = S$;
and for R^1 being 2,4-difluorophenyl, 2,3-dichlorophenyl, 2,6-dimethylphenyl, 2,6-di(methylethyl)-phenyl R^2 is amino, and $X = O, S$.

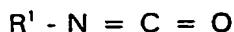
2. A method of preparing 1,3-disubstituted ureas of general formula I according to claim 1, characterized in that an amine of general formula II,

AMENDED SHEET (ARTICLE 19)



II

wherein R² and X have the above defined meanings, is treated with an isocyanate of general formula III,



III

wherein R¹ has the above defined meaning, said isocyanate optionally being formed in situ from appropriate reactants,

thus giving the above defined urea.

3. The method of claim 2, characterized in that when said isocyanate is formed in situ, the reaction is carried out in toluene at about 80°C.

4. The method of any of the preceding claims, characterized in that the obtained 1,3-disubstituted urea of general formula I wherein R² means nitro, is treated with hydrogen in the presence of palladium catalyst to reduce the nitro group to the amino group.

5. 1,3-Disubstituted ureas of general formula I, according to claim 1 and/or prepared by the method of claim 2 to 4, characterized in that they have inhibitory effect on the acyl co-enzyme A:cholesterol acyltransferase (ACAT) enzyme.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/SK 98/00019

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C275/36 C07C323/44 C07D213/75 //A61K31/17, A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 284 433 A (H. J. BECKER ET AL) 8 November 1966 see claims 6,8 see examples	1,2
X	EP 0 709 225 A (NIPPON PAPER INDUSTRIES CO) 1 May 1996 see page 15, line 35	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

31 March 1999

12/04/1999

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Van Geyt, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/SK 98/00019

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 3284433	A	08-11-1966	CH 459174 A DE 1468337 A FR 1469459 A GB 1068887 A	28-11-1968 10-05-1967
EP 0709225	A	01-05-1996	JP 8118806 A JP 8156407 A CA 2161376 A DE 69503864 D DE 69503864 T US 5710094 A	14-05-1996 18-06-1996 28-04-1996 10-09-1998 18-03-1999 20-01-1998